Claims 1 and 3 have been amended and new claims 62-71 have been added to divide natural and artificial insults into two claim groups for ease of prosecution; the scope of the claims as a whole has not been changed by these amendments.

Claims 27 and 33 have been amended to more particularly point out and distinctly claim embodiments of the invention. The scope of these claims has not been changed by these amendments.

New claims 46-61 have been added to more particularly point out and distinctly claim embodiments of the invention related to the embodiments of the claims remaining after the restriction requirement.

These amendments, cancellations, and additions are fully supported by the application as-filed, and no new matter is added. Claims 1- 23, 27-36, and 46-71 are currently pending.

Claims 1-36 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over "Apoptosis-associated signaling pathways are required for chemotherapy-mediated female germ cell destruction" authored by Perez *et al.* ("Perez") in view of U.S. Patent No. 5,712,262 to Spiegel ("Spiegel") and further in view of U.S. Patent No. 5,877,167 to Igarashi *et al.* ("Igarashi"). This ground of rejection, insofar as the Examiner may consider it applicable to any claim in this application upon entry of the present amendment, is respectfully traversed and reconsideration thereof is respectfully requested. Applicants also assert that new claims 46-71 are patentable over the references, alone or in any combination, for at least the same reasons that Claims 1- 23 and 27-36 are patentable over any of the references alone or in any combination.

Rejection of Claims 1-36 Under 35 U.S.C. §103(a)

Claims 1-36 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Perez in view of Spiegel and further in view of Igarashi. The Office Action concludes that the present invention allegedly would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Applicants respectfully submit that a *prima*

facie case of obviousness has not been established for at least the following reasons.

The pending claims are directed to methods of protecting a female reproductive system from natural insults or from artificial insults, such as damage caused by treatment for a disease, disorder, or condition; preserving, enhancing, or reviving ovarian function in mammals; and preventing or ameliorating menopausal syndromes in women comprising administration of an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products. Each of the claims requires that the agent be administered in one of the following amounts: an amount effective to protect the female reproductive system from destruction caused by an artificial insult; an amount effective to preserve, enhance, or revive ovarian function; an amount effective to prevent or ameliorate at least one menopausal syndrome; an amount effective to protect a female reproductive system from destruction caused by a chemical treatment, radiological treatment, surgical treatment, or combination; or an amount effective to protect a female reproductive system from pre-mature aging or destruction caused by a natural insult.

None of Perez, Spiegel, or Igarashi, either alone or in combination renders these claims obvious. In fact, none of the references, either alone or in any combination, provides an enabling disclosure of the present invention or teaches or suggests all of the limitations of the claims.

With regard to all claims and particularly regarding claims to protection of a female reproductive system from artificial insults (such as claims 1 and 46 and claims dependent therefrom), it is particularly significant that Perez's studies on the effects of sphingosine-1-phosphate (S1P) on the survival of oocytes exposed to doxorubicin are performed in *in vitro* cultures of oocytes. See, Perez, p. 1229, col. 1, lines 21-26. It is a commonly accepted principle that success *in vitro* does not provide a reasonable expectation of success *in vivo* or *ex vivo*. Such *in vitro* studies, at most, make it obvious to try to prevent damage to a female reproductive system from doxorubicin by administering S1P. Obviousness to try is not a proper standard for finding a claim obvious under 35 U.S.C. §103(a).

Further, Perez itself makes clear that the results of the *in vitro* study on oocytes presented in the reference do not establish a reasonable expectation of success *in vivo* or *ex vivo*, in ovaries, or in a reproductive system. For example, Perez points out that "fertility preservation would require maintenance of the entire follicle and not solely the oocyte." Perez, page 1230, col. 1, lines 6-7.

With regard to claims to protection of a female reproductive system from natural insults; preventing or ameliorating menopausal syndromes in women; and preserving, enhancing, or reviving ovarian function (such as claims 62, 33, and 27 and claims dependent therefrom), Perez makes no teaching or suggestion that treatment with S1P would be capable of achieving such goals. Nowhere does Perez even mention the use of S1P for such treatments.

Additionally, as Perez fails to enable and/or even suggest *in vivo* or *ex vivo* protection from artificial insults; protection of ovaries; protection of the reproductive system; protection from natural insults; preserving, enhancing, or reviving ovarian function; or preventing or ameliorating menopausal syndromes, Perez necessarily fails to teach or suggest the limitations, one of which is present in each independent claim, that an agent be administered in an amount effective to protect a female reproductive system from destruction caused by an artificial insult (Claim 1); to preserve, enhance, or revive ovarian function (Claim 27); to prevent or ameliorate at least one menopausal syndrome (Claim 33); to protect the reproductive system from destruction caused by a chemical treatment, radiological treatment, surgical treatment or combination (Claim 46); or to protect a female reproductive system from pre-mature aging or destruction caused by a natural insult (Claim 62).

As these limitations are also neither taught nor suggested in Spiegel or Igarashi, Perez in combination with either or both of Spiegel or Igarashi fails to teach all limitations of the claims, and a *prima facie* case of obviousness has not been established.

Spiegel does not teach or suggest protecting a female reproductive system from insults, be they natural or artificial; nor does it teach or suggest preventing damage from a

treatment, such as chemical treatment, radiological treatment, surgical treatment, and combinations thereof used to treat a disease, disorder, or condition. Likewise, Spiegel neither teaches nor suggests preserving, enhancing, or reviving ovarian function in mammals or preventing or ameliorating menopausal syndromes in women. In fact, Spiegel neither teaches nor suggests anything about the female reproductive system. Instead, Spiegel focuses on epidermal cells and neurodegenerative diseases. Thus, Spiegel neither teaches nor suggests the methods of the present invention and fails to teach or suggest the claim limitations lacking in Perez.

Additionally, Spiegel provides only *in vitro* results, and therefore suffers from the same deficiencies as Perez; even as to epidermal and neurodegenerative disorders, Perez dpes not provide any reasonable expectation of success of treatment *in vivo* or *ex vivo*.

Likewise, Igarashi does not teach or suggest protecting a female reproductive system from insults, be they natural or artificial; nor does it teach or suggest preventing damage from a treatment, such as chemical treatment, radiological treatment, surgical treatment, and combinations thereof used to treat a disease, disorder, or condition. Like Spiegel, Igarishi neither teaches nor suggests preserving, enhancing, or reviving ovarian function in mammals or preventing or ameliorating menopausal syndromes in women. Again like Spiegel, Igarishi neither teaches nor suggests anything about the female reproductive system.

Significantly, Igarashi fails to teach or suggest the claim limitations lacking in Perez. Although Igarashi may teach dosing information, as the Action suggests, the dosing information is irrelevant to the present invention.

Thus, neither Spiegel nor Igarashi provide the reasonable expectation of success lacking in Perez. Further, they do not teach or suggest the claim limitations lacking in Perez.

Furthermore, there is no motivation to combine the references. There is no motivation to combine Perez and Spiegel because Perez relates to damage to oocytes by cancer treatments and Spiegel relates to prevention of damage caused by aging and degenerative

diseases. Thus, Spiegel and Perez do not address treatment of the same condition. Igarashi addresses the prevention of metastasis, chemoinvasion, cell motility, and inflammation, which are all conditions that are very different from those addressed by either Perez or Spiegel.

For at least these reasons, Claims 1, 27, 37, 46, and 62 are unobvious over Perez, Spiegel, and Igarashi, taken alone or in any combination. Claims 2-23, 28-36, 47-61, and 63-71 are likewise unobvious over the references, at least because they depend either directly or indirectly from Claims 1, 27, 37, 46, or 62

CONCLUSION

Applicants submit that the subject application is in condition for allowance, and respectfully request that such action be taken. Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attachment is captioned "Version with Markings to Show Changes Made." The Examiner is invited to contact Deborah Somerville, Esq. at (212)-908-6142 of Kenyon & Kenyon, New York, N.Y. to discuss any matter regarding this application.

Respectfully submitted,
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Dated: 10 apr 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of protecting a female reproductive system against [a natural or] an artificial insult comprising: administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (*ASMase*) gene products, in an amount sufficient to protect said female reproductive system from [pre-mature aging or] destruction caused by said [natural or] artificial insult, wherein said administration is *in vivo* or *ex vivo*.

3. (Amended) The method of claim [1] 62 wherein said natural insult is a consequence of aging, genetic background, physiological factors, environmental factors, or a combination thereof.

27. (Amended) A method of preserving, enhancing, or reviving ovarian function in mammals comprising: administering [to said mammal an effective amount of] a composition comprising sphingosine-1-phosphate, or an analog thereof to said mammal in an amount effective to preserve, enhance, or revive ovarian function .

33. A method of preventing or ameliorating menopausal syndromes in women, comprising administering to women, at predetermined intervals, a composition comprising sphingosine-1-phosphate, or an analog thereof in an amount effective to prevent or ameliorate at least one menopausal syndrome.